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Emerging Multidrug Resistance of Methicillin-Resistant *Staphylococcus aureus* in Hand Infections

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Background: Methicillin-resistant *Staphylococcus aureus* has been the most commonly identified pathogen in hand infections at urban centers, but the evolving antibiotic sensitivity profiles of methicillin-resistant *Staphylococcus aureus* are not known. The purposes of this study are to determine if multidrug resistance in methicillin-resistant *Staphylococcus aureus* is emerging and to provide current recommendations for empiric antibiotic selection for hand infections in endemic regions.

Methods: An eight-year longitudinal, retrospective chart review was performed on all culture-positive hand infections encountered by an urban hospital from 2005 to 2012. The proportions of all major organisms were calculated for each year. Methicillin-resistant *Staphylococcus aureus* infections were additionally analyzed for antibiotic sensitivity.

Results: A total of 683 culture-positive hand infections were identified. Overall, methicillin-resistant *Staphylococcus aureus* grew on culture in 49% of cases; the annual incidence peaked at 65% in 2007. Over the study period, methicillin-resistant *Staphylococcus aureus* was universally resistant to penicillin, oxacillin, and ampicillin. Clindamycin resistance significantly increased, approaching 20% by 2012 ($p = 0.02$). Levofloxacin resistance linearly increased from 12% to 50% ($p < 0.01$). Resistance to trimethoprim-sulfamethoxazole, tetracycline, gentamicin, and moxifloxacin was only sporadically observed. Resistance to vancomycin, daptomycin, linezolid, and rifampin was not observed.

Conclusions: Significant increases in resistance to clindamycin and levofloxacin were observed in recent years, and empiric therapy with these drugs may have limited efficacy, especially in urban centers.

Clinical Relevance: Hand infections caused by methicillin-resistant *Staphylococcus aureus* may be developing increasing resistance to clindamycin and levofloxacin in recent years. This longitudinal study examines the effectiveness of a variety of antibiotics to methicillin-resistant *Staphylococcus aureus*.

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Staphylococcus aureus is the most commonly cultured organism in hand infections¹⁻⁶. Traditional management of acute hand abscesses has been incision and drainage followed by a regimen of beta-lactam antibiotics such as methicillin, nafcillin, or cephalosporins^{1,2}. However, shortly following the introduction of methicillin in the 1960s, emerging strains of methicillin-resistant *Staphylococcus aureus* (MRSA) were reported as first occurring in the nosocomial setting and more recently in the community setting³⁻¹⁰. As MRSA has been more

closely monitored, studies have noted associations with increased treatment failures, inpatient lengths of stay, and health-care costs^{4,7,8,11,12}. However, a few recent reports have suggested that treatment failures, costs, and lengths of stay may be equivalent to non-MRSA infections if an appropriate empiric antibiotic is selected^{4,6}.

As a result of multiple reports showing a greater prevalence of MRSA in urban settings, the Centers for Disease Control and Prevention have recommended against selecting a

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given empiric antibiotic if the local resistance is greater than 10% to 15%, and many institutions have now subsequently excluded beta-lactams from empiric treatment^{4,13,14}. However, the efficacy of contemporary empiric drug selections is not known, and the possibility of growing multidrug resistance exists, as alternative antibiotics are becoming more commonly selected to cover MRSA. The purposes of this study are to determine if multidrug resistance in MRSA is emerging and to provide current evidence that clinicians can reference for empiric inpatient or outpatient treatment of hand infections.

Materials and Methods

A retrospective study was performed at an urban academic medical center over an eight-year period from January 1, 2005, through December 31, 2012. After approval was obtained from the institutional review board, all hand infection cases encountered by the emergency room, outpatient office, or inpatient wards were reviewed. We identified subjects by searching International Classification of Diseases, Ninth Revision, codes relevant to hand infections, including codes 681.00, 681.01, 681.02, 682.4, 727.05, 727.9, 883.00, 883.1, 882.01, and 882.00 (cellulitis, abscess, tenosynovitis, and open wounds of the fingers and hands) but only analyzed those subjects between the ages of eighteen and eighty-nine years with a culture-positive hand abscess. Demographic and laboratory data were collected from medical records. Patients with multiple culture results in the same admission were also identified so that the same organism was not counted twice. Infections were considered nosocomial if records indicated a history of a surgical procedure, dialysis treatments, catheterizations, hospitalization, or nursing home stays within a year prior to admission.

We calculated the annual frequencies of culture-positive infections for the three most common isolates (MRSA, methicillin-sensitive *Staphylococcus aureus* [MSSA], and *Streptococcus pyogenes*) and polymicrobial infections. A polymicrobial infection was defined as an infection in which more than one organism was identified; these were not considered mutually exclusive with the frequencies of other organisms. MRSA infections were then further analyzed for their antibiotic sensitivity profiles. Isolates were assessed for yearly resistance rates to ampicillin, oxacillin, penicillin, clindamycin, erythromycin, levofloxacin, moxifloxacin, trimethoprim-sulfamethoxazole, tetracycline, gentamicin, rifampin, daptomycin, vancomycin, and linezolid. We also performed a post hoc calculation for MSSA resistance to clindamycin and levofloxacin.

Statistical Analysis

Continuous variables were assessed with a linear regression model. Percentages of categorical variables and drug resistances were assessed for a significant increasing or decreasing trend with the Cochran-Armitage trend test. Significance was defined as $p < 0.05$.

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No external source of funding was used for this study.

Results

Overall Demographic Characteristics

A total of 683 culture-positive hand infections were identified over the ninety-six-month collection period. The average patient age was 41.4 years, and 56% were male; the average white blood cell count was $10.8 \times 10^3/\mu\text{L}$. The most common etiologies for cases were trauma (75%) and intravenous drug use (21%); bite wounds were causative in 3% of cases. The average annual frequency of comorbidities was consistent over the study period for patients with diabetes (14.6% [range, 12.6% to 28.6%] of the population) and for patients who were positive for the human immunodeficiency

TABLE I Organisms Grown on Culture from Specimens from Acute Hand Infections, 2005 to 2012

Most common organisms
MRSA (49%)
MSSA (21%)
Polymicrobial (20%)
<i>Streptococcus pyogenes</i> (8%)
Least common organisms
<i>Acinetobacter baumannii</i>
<i>Acinetobacter calcoaceticus</i>
<i>Aspergillus</i> species
<i>Bacillus</i> species
<i>Candida albicans</i>
<i>Candida parapsilosis</i>
<i>Citrobacter freundii</i>
Diphtheroid species
<i>Eikenella corrodens</i>
<i>Enterobacter cloacae</i>
<i>Enterococcus faecalis</i>
<i>Escherichia coli</i>
<i>Haemophilus parainfluenzae</i>
<i>Klebsiella pneumoniae</i>
<i>Lactobacillus</i> species
<i>Leclercia adecarboxylata</i>
<i>Mycobacterium avium</i> complex
<i>Pasteurella multocida</i>
<i>Porphyromonas gingivalis</i>
<i>Proteus mirabilis</i>
<i>Pseudomonas aeruginosa</i>
<i>Serratia marcescens</i>
<i>Staphylococcus</i> (coagulase-negative)
<i>Staphylococcus epidermidis</i>
<i>Streptococcus</i> (alpha-hemolytic)
<i>Streptococcus anginosus</i>
<i>Streptococcus constellatus</i>
<i>Streptococcus</i> (Groups B, C, F, and G)
<i>Streptococcus intermedius</i>
<i>Streptococcus mitis</i>
<i>Veillonella</i> species

virus (3.3% [range, 0% to 5.7%] of the population). However, intravenous drug users represented a larger percentage of people with culture-positive hand infections over the time span of the study: 13.8% in 2005 and 37.2% in 2012 ($p < 0.01$). Patients with a history of cancer or nursing home residence were each noted in approximately 2% of all hand infections. MRSA infections were considered to be community acquired in 76% of cases and nosocomial in 24% of cases.

Organisms Grown on Culture per Annum

Overall, MRSA was the organism most commonly grown on culture, followed by MSSA and then Group A *Streptococcus*. A variety of organisms were found in lesser frequencies (Table I). MRSA was also the most common pathogen identified during

TABLE II Annual Resistance of MRSA to Selected Antibiotics

Antibiotic	Annual Resistance								P Value*
	2005	2006	2007	2008	2009	2010	2011	2012	
Ampicillin	100%	100%	100%	100%	100%	100%	100%	100%	1
Oxacillin	100%	100%	100%	100%	100%	100%	100%	100%	1
Penicillin G	100%	100%	100%	100%	100%	100%	100%	100%	1
Erythromycin	100%	90%	98%	94%	85%	96%	100%	92%	0.59
Levofloxacin	12%	22%	37%	39%	33%	41%	43%	50%	<0.01
Clindamycin	7.0%	6%	9%	4%	6%	19%	13%	20%	0.02
Tetracycline	2%	0%	2%	3%	6%	0%	3%	0%	0.97
Moxifloxacin	0%	3%	8%	0%	0%	0%	0%	3%	0.17
Trimethoprim-sulfamethoxazole	0%	0%	0%	0%	4%	5%	3%	0%	0.14
Gentamicin	0%	0%	0%	0%	5%	0%	0%	0%	0.50
Rifampin	0%	0%	0%	0%	0%	0%	0%	0%	1
Vancomycin	0%	0%	0%	0%	0%	0%	0%	0%	1
Linezolid	0%	0%	0%	0%	0%	0%	0%	0%	1
Daptomycin	0%	0%	0%	0%	0%	0%	0%	0%	1

*Significance was set at $p < 0.05$.

every year of the study, and it grew on culture in the following proportions: 53% in 2005, 63% in 2006, 65% in 2007, 43% in 2008, 47% in 2009, 45% in 2010, 37% in 2011, and 42% in 2012 (Fig. 1). The number of MSSA infections fluctuated inversely, with MRSA reaching a nadir in 2006 and 2007 but increasing to a peak of 27.5% in 2012. A significant increase ($p < 0.01$) was observed in the percentage of polymicrobial infections, as they comprised 7% in 2005, 16% in 2006, 13% in 2007, 30% in 2008, 31% in 2009, 36% in 2010, 37% in 2011,

and 25% in 2012. *Streptococcus pyogenes* infections were grown on culture in 6% to 17% of cases per year.

For intravenous drug users and diabetic patients with hand infections, MRSA remained the most common organism each year, reaching a peak incidence in 2007 as well. Intravenous drug users had the highest annual percentages of MRSA of all subgroups. Diabetic patients with hand infections commonly had polymicrobial infections (33% overall [range, 22% to 50% per year]), but this percentage did not increase over

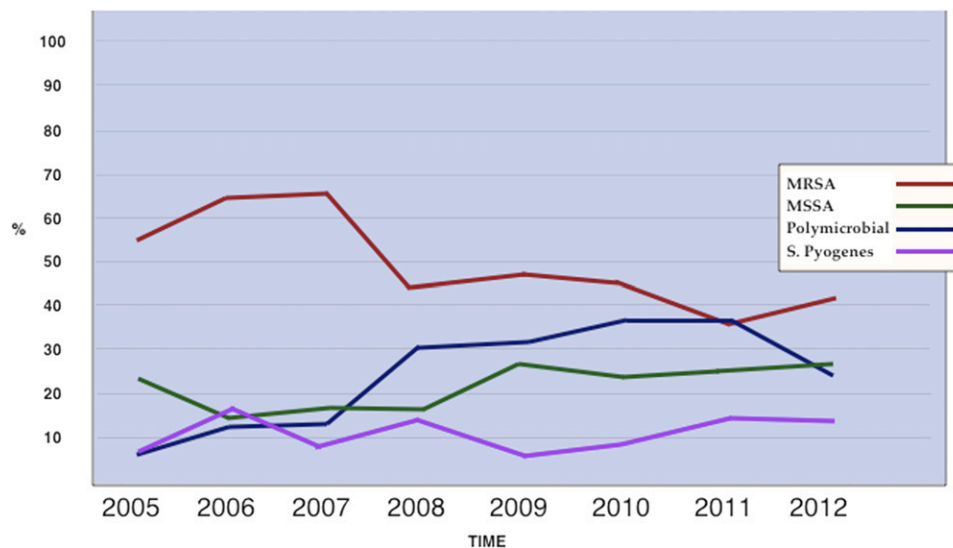


Fig. 1

The annual percentages of MRSA, MSSA, polymicrobial organisms, and *Streptococcus pyogenes* grown on culture from specimens from acute hand infections.

time. Intravenous drug abusers and people without comorbidities who had hand infections showed increases in polymicrobial infections over time ($p < 0.01$). Intravenous drug users had polymicrobial organisms that grew on culture in 8% of cases in 2005, and this percentage increased to 35% of cases in 2010 and declined to 20% of cases in 2012.

Staphylococcus aureus Antibiotic Sensitivity Profiles per Annum

MRSA resistance to clindamycin significantly increased over the eight-year period ($p = 0.02$); the three highest percentages were found from 2010 to 2012 as resistance approached 20% (Table II). MSSA resistance to clindamycin did not increase significantly over the study period but was present in 11% of culture specimens overall (range, 8% to 12% per year). MRSA resistance to levofloxacin linearly increased over eight years from 12% to 50% ($p < 0.01$). MSSA resistance to levofloxacin did not significantly increase ($p = 0.68$) over the study period but was present in 12% of culture specimens overall (range, 9% to 17% per year). Over the eight years studied, MRSA was uniformly resistant to ampicillin, oxacillin, and penicillin G; erythromycin resistance was also common and ranged from 85% to 100% per year. MRSA was only sporadically resistant to tetracycline, moxifloxacin, trimethoprim-sulfamethoxazole, and gentamicin. No resistance was observed for rifampin, vancomycin, linezolid, or daptomycin.

Discussion

MRSA has gained attention in the literature and in popular media as a growing concern, especially in urban environments, as several reports have estimated a high proportion in hand abscesses ranging from 34% to 73%^{4,12-18}. Our results agree with prior studies and indicate that MRSA may be found

in approximately half of all hand infections in urban communities in recent years. Moreover, increased costs, failures in treatment, and increased mortality have also been associated with MRSA in endemic regions^{4,6-9,11,12}; however, multiple studies from our institution have shown that equivalent lengths of hospital stay to non-MRSA infections can be achieved if appropriate empiric antibiotic coverage is selected^{4,6}. As MRSA continues to predominate in urban communities, we sought to further characterize its antibiotic sensitivities to optimize the empiric treatment regimen, to reduce treatment delays, and to improve cost containment associated with hand infections.

MRSA grown on culture from specimens from hand infections was increasingly resistant to clindamycin and levofloxacin over the eight-year period, and the sensitivity to other antibiotics did not appear to change. In recent years, MRSA resistance to clindamycin has approached 20% at our center. Although not directly answered by the present study, we suspect that the increased use of clindamycin to treat MRSA may be contributory. In 2005, we adopted a hand infection algorithm to improve the coverage of MRSA, which largely excluded beta-lactams from empiric treatment of hand infections^{4,8}. Therapeutics such as vancomycin, clindamycin, and trimethoprim-sulfamethoxazole were used with a much greater frequency, and, in particular, clindamycin was the most commonly prescribed initial antibiotic for hand infections, representing 40% to 50% of the empiric selections from 2005 to 2007.

In addition, levofloxacin resistance linearly increased over the past eight years in our study. A report by MacDougall et al. noted a significant association between emerging MRSA infections and quinolone prescriptions in a cross-sectional study of seventeen regional U.S. hospitals; the authors suggested that quinolones may be driving a selection process for MRSA, but their conclusions were limited in that the MRSA resistance to

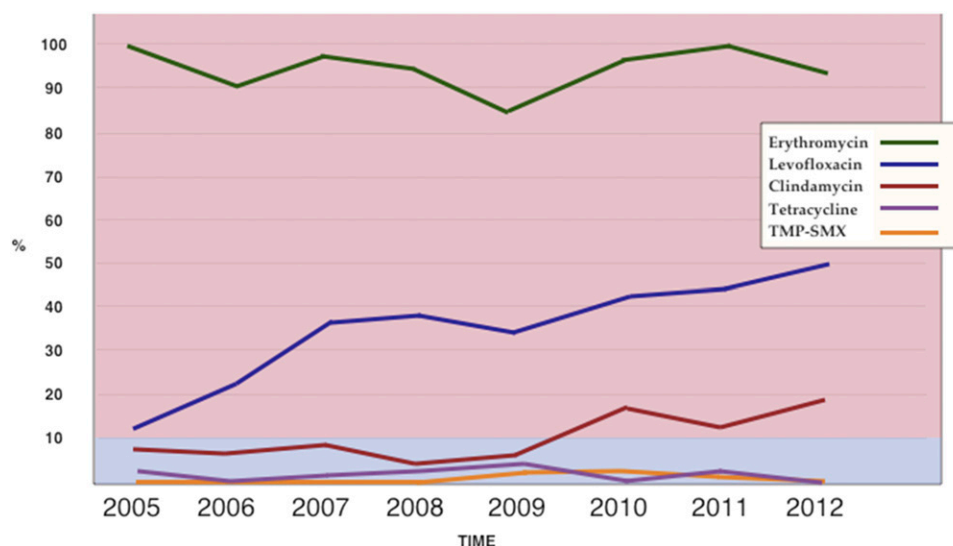


Fig. 2
Multidrug resistance in MRSA by year. The region shaded in pink represents an unacceptable resistance level for use in empiric coverage as defined by the Centers for Disease Control and Prevention. Antibiotics found to have 100% resistance or sensitivity are not displayed. TMP-SMX = trimethoprim-sulfamethoxazole.

quinolones was not known¹⁹. Although levofloxacin is not commonly prescribed for hand infections, some reputable sources suggest “fluoroquinolones” as an alternative to penicillin-based drugs in the presence of an allergy²⁰. Our results suggest that levofloxacin would not be a wise choice in this class, but moxifloxacin appeared to be an effective quinolone with only sporadic cases of resistance observed in this series.

Despite the narrowing of antibiotic choices, MRSA infections still remain consistently sensitive to a number of therapeutics. Tetracycline, gentamicin, moxifloxacin, and trimethoprim-sulfamethoxazole were resistant in only a few cases in our study, and no resistance was observed for vancomycin, daptomycin, linezolid, and rifampin. Vancomycin intermediate resistance in *Staphylococcus aureus* has been sparsely reported in the literature, but, to the best of our knowledge, no cases of vancomycin-resistant MRSA have occurred in hand infections⁸. Despite frequent use, vancomycin still remains an effective first-line agent for the empiric treatment for hand infections.

The present study had several limitations. The retrospective design limited the patients whom we were able to identify. Additionally, our local prevalence of MRSA may be dissimilar to non-urban medical centers, and our results may not be generalized to other regions. Further, the number of polymicrobial infections may have been overestimated, as some culture specimens were obtained in a non-sterile environment. We were not able to accurately retrieve the number of culture specimens obtained by bedside procedures; however, we routinely attempt to reduce contamination during bedside procedures with sterile draping and chlorhexidine-alcohol skin preparation prior to incision.

Infections caused by MRSA have a substantial presence, especially in urban areas²¹. In our region, MRSA was found in nearly half of all hand infections, and those isolates became increasingly resistant to clindamycin and levofloxacin over the study period. As a result, we would not recommend these drugs as empiric antibiotics to clinicians who practice in endemic areas with a significant prevalence of MRSA. The Centers for Disease Control and Prevention do not recommend antibiotics for empiric therapy that have a regional resistance that exceeds 10% (Fig. 2)²². However, other therapeutics such as vancomycin, tetracycline, moxifloxacin, and trimethoprim-sulfamethoxazole

still appear to have potent activity against MRSA. Organisms that grew on culture from specimens from polymicrobial infections were often sensitive to most antibiotics, and we would not recommend empiric treatment for anaerobic or gram-negative bacteria unless specific situations such as bite wounds, aquatic injuries, or severe infections warranted such coverage. In this series, infections caused by bite wounds were generally susceptible to beta-lactam antibiotics, which may be selected in an empiric management protocol under these circumstances. Finally, we would encourage future studies evaluating the efficacy of common empiric antibiotics in other soft-tissue and joint infections of the extremities with interval monitoring to ensure relevant and current management recommendations. ■

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